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7 August 2006

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Dear Dr Longson

APPRAISAL CONSULTATION DOCUMENT (ACD): BORTEZOMIB FOR MULTIPLE MYELOMA

Thank you for providing Ortho Biotech with an opportunity to comment on the ACD. Contrary to the position articulated in the ACD, it is our assertion that the APEX trial has established bortezomib as the evidence-based standard of care for patients with relapsed multiple myeloma (MM). Consequently, we believe that the Appraisal Committee's provisional recommendation is unsound and does not constitute a suitable basis for the preparation of guidance to the NHS. We acknowledge that this decision has been reached because the Appraisal Committee requires further clarification on three issues.

1. A perceived lack of clarity around the role of bortezomib in the MM treatment pathway.
2. A concern around the clarity and detail in the reporting of the APEX trial.
3. Concerns with the economic model, resulting in the conclusion that bortezomib "had not been shown to be cost-effective compared with clinical practice in the NHS".

The attached report provides comprehensive clarification on these issues to help the Appraisal Committee fully understand the data supporting the clinical and cost-effectiveness of bortezomib. The key points covered in the attached report are summarised briefly below.

Lack of clarity around the role of bortezomib in the MM treatment pathway

- There are defined treatment pathways for myeloma, but because of the heterogeneous nature of the disease and its clinical course, the choice of treatment for each patient at any one time may differ. Thus, treatment must be individualised.
- The APEX trial has established bortezomib as the evidence-based standard of care for patients with relapsed MM. In APEX, the bortezomib group had higher response rates, increased time to progression and better survival versus high dose dexamethasone (HDD). The clear superiority of bortezomib over HDD meant that trial had to be halted prematurely because it was deemed unethical to continue.

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- APEX is the largest, peer-reviewed, published RCT in relapsed MM. This level one evidence is endorsed by the ERG as being of "reasonable quality".
- APEX established that bortezomib is most effective when used at first relapse. Bortezomib treatment at first relapse resulted in improved survival, time to progression and overall response rate compared to use at 2nd relapse and beyond. This positioning is endorsed in the British Committee on Standards in Haematology guideline.
- Failure to recommend use of bortezomib in routine management means that patients will have to rely on unlicensed, unproven treatments such as thalidomide.
- Although thalidomide is commonly used in relapsed MM (and increasingly in front-line), the optimal dosing schedule of this completely unlicensed treatment has never been established and there are no thalidomide monotherapy RCTs in this patient group[1]. Given this complete lack of published thalidomide RCTs, robust, meaningful comparisons with bortezomib are not possible. We agree with the ERG's conclusion that HDD is the only relevant comparator.

Concern around the lack of clarity in detail in the reporting of the APEX trial

- The ACD states that "*lack of clarity and detail in reporting the APEX RCT made the interpretation of clinical effectiveness difficult*". However, the ERG actually concludes, "**these limitations do not significantly affect the overall results especially in light of clarifications received from the manufacturer**" and we question why this important clarification was omitted from the ACD.

Concerns with the economic modelling approach

- The ERG critique of our economic model was largely fair and balanced and we note their conclusion that ***"In general the approach taken to model disease progression and cost-effectiveness in this patient group seems reasonable".*** We question why this important comment was omitted from the ACD.
- HDD is the only relevant comparator for the economic model. As stated above, thalidomide is commonly used in the UK, but it is not possible to robustly model its cost-effectiveness due to a complete lack of thalidomide RCTs in relapsed MM and uncertainty around its optimal dosing. Reasons for discounting other possible comparators are fully described in the main response document.
- To ensure that the economic evaluation of bortezomib is fit for purpose, we have updated the model in line with ERG comments. Most importantly, QALYs are now fully integrated into the model.
- Results of the updated analysis shows that when bortezomib is used at 1st relapse, with implementation of a 3-cycle stopping rule for non-responders, the cost per QALY is £33,500. When dexamethasone is added to bortezomib to boost response, the cost per QALY is £30,500.
- This updated analysis validates the ERG findings that bortezomib is most cost-effective when used at 1st relapse and when treatment is stopped after three cycles in non-responders. Combination with dexamethasone, (a strategy that is mentioned within the Velcade SmPC) decreases the cost per QALY even further.

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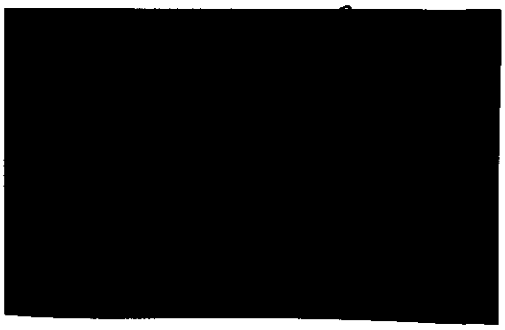
[1] Glasmacher et al. A systematic review of phase II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. British Journal of Haematology 2005; 132: 584-593

In conclusion, the APEX trial established bortezomib as the evidence-based standard of care for patients with relapsed MM and in doing so, clarified its appropriate place in the treatment pathway. The ACD recommendation to use bortezomib only in clinical trials is therefore not appropriate, because APEX has already successfully answered this question.

Bortezomib patients had superior response rates, increased time to progression and survival compared to HDD and the benefits were most pronounced in patients who received it at first relapse. Our revised economic analysis confirms that bortezomib is most cost-effective when used at 1st relapse and when treatment is limited to three cycles in non-responders. Combination with dexamethasone further enhances response rates and cost-effectiveness.

Ortho Biotech believes that the available evidence supports guidance recommending the use of bortezomib as a treatment option for appropriate patients at first relapse. Implementation of a stopping rule and consideration of co-administration with dexamethasone can help ensure that Velcade treatment is a cost-effective use of scarce NHS resources.

Yours sincerely



ORTHO BIOTECH COMMENTS ON THE APPRAISAL CONSULTATION DOCUMENT (ACD): BORTEZOMIB FOR MULTIPLE MYELOMA

As requested we have structured our comments using the headings suggested in your letter dated 17th July.

WHETHER YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST-EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE

We believe that three areas of concern drove the Appraisal Committee's provisional recommendation:

1. A perceived lack of clarity around the role of bortezomib in the multiple myeloma (MM) treatment pathway.
2. A concern around the clarity and detail in the reporting of the APEX trial.
3. Concerns with the economic model, resulting in the conclusion that bortezomib "had not been shown to be cost-effective compared with clinical practice in the NHS".

We provide comments on each of these three specific issues below.

THE APPRAISAL COMMITTEE INDICATE A PERCEIVED LACK OF CLARITY AROUND THE ROLE OF BORTEZOMIB IN THE MULTIPLE MYELOMA TREATMENT PATHWAY.

We contend however that Bortezomib is clearly established as the evidence-based standard of care for patients at 1st relapse

1.1 The Appraisal Committee is incorrect in stating that treatment pathways for multiple myeloma (MM) are poorly defined. Treatment pathways do exist and are clearly documented in clinical guidelines. Most notable from a UK context are the 2005 guidelines developed by the British Committee on Standards in Haematology (Smith et al 2005, updated with Morgan et al 2005), which is a subgroup of the British Society for Haematology. This committee recommends that Bortezomib is available for clinicians to use in accordance with its licence, ie in patients with relapsed myeloma. Although guidelines are helpful, MM is a heterogeneous and incurable disease and therefore patients need access to different treatment options at different times during the course of their disease. We would recommend therefore that the Appraisal Committee carefully consider the unique characteristics of MM and its treatment and that it actively works to understand these complex issues through dialogue with relevant professional bodies such as the UKMF, BCSH and Royal College of Pathologists.

1.2 Bortezomib represents a significant advance in the treatment of MM and is the only new licensed treatment for this disease in over a decade. It is also the only agent specifically licensed for relapsed myeloma. The unprecedented data seen in the phase II SUMMIT and CREST trials, confirmed in the phase III APEX trial, are due to bortezomib's unique mechanism of action, that of intra-cellular proteasome inhibition. This is a fundamentally different mechanism from current chemotherapy options, hence bortezomib is also active in patients who have

resistance to previous therapy. The proteasome is fundamental to the survival of myeloma cells, thus, bortezomib's targeted effect on the proteasome translates into significant clinical efficacy by directly inducing cell death.

1.3 Section 1.1 of the ACD suggests that there is a need for additional trials to establish the position of bortezomib in the pathway of care for people with MM. We strongly disagree with this statement and believe that there is certainty around where bortezomib should be used in the MM treatment pathway. This is because the APEX trial (Richardson et al, 2005), established bortezomib as the evidence-based standard of care for patients with relapsed MM. The APEX trial is the largest, peer-reviewed RCT ever to have been published in patients with relapsed MM. This means that bortezomib is supported by level one evidence from an RCT that the ERG rates as being of "reasonable quality" when judged against standard NICE quality criteria. The APEX trial confirmed that bortezomib improved response rates and increased time to progression and survival compared to high dose dexamethasone (HDD) in patients with MM at first relapse and beyond. This result demonstrated that bortezomib is a highly effective treatment in relapsed myeloma relative to the only other treatment (HDD) licensed for use in this population.

1.4 The APEX trial also precisely clarifies bortezomib's place in the treatment pathway. When data were analysed according to whether patients received treatment at 1st relapse compared to second relapse and beyond, (Sonneveld et al, 2005), results show that the patients treated at 1st relapse had increased time to progression, survival and higher response rates. This clearly shows that there is greater benefit derived from bortezomib for patients at 1st relapse rather than later in the treatment pathway, and provides NICE with clear evidence on how to ensure that bortezomib is used most effectively in the NHS. A consensus has also emerged within the clinical community on this issue. As previously mentioned, the BCSH who aim to provide haematologists with evidence based guidelines using a well-defined development process, support the use of bortezomib at 1st relapse on the basis of the APEX study (Morgan et al, 2005). Most recently, another recognised government sponsored guideline development group, Cancer Care Ontario (http://www.cancercare.on.ca) have recommended bortezomib as the preferred treatment option for relapsed MM: *"For patients with myeloma refractory to or relapsing within one year of the conclusion of initial or subsequent treatment(s) (including autologous stem cell transplantation) who are candidates for further chemotherapy, bortezomib is recommended as the preferred treatment option*" (Reece et al, 2006).

1.5 The addition of dexamethasone to bortezomib in patients with relapsed and/or refractory myeloma, who had suboptimal responses to bortezomib alone, was associated with improvement in responses without prohibitive toxicity. In the CREST study in particular, where patients presented after failing only one prior treatment regimen, a 12% increase in overall response was seen with the addition of dexamethasone (Jagannath et al 2004). These findings represent clinical validation of the additional benefit from the combination of bortezomib with dexamethasone, as demonstrated in preclinical models (Hideshima et al, 2001). The use of combination therapy is a well-established principle in the treatment of cancer, hence addition of dexamethasone to enhance response rates with bortezomib is not unexpected, and has been shown to be effective and

well tolerated as evidenced by its inclusion in section 5.1 of the SmPC for Velcade (bortezomib). Consequently the addition of HDD to bortezomib monotherapy is now established as routine by many clinicians in the UK.

1.6 Ortho Biotech notes that the ACD appears contradictory on the issue of licence status. The ACD whilst acknowledging that thalidomide, a treatment that has no marketing authorisation in the UK, is commonly used in clinical practice, it is however also suggested that it [thalidomide] could have been a comparator in this appraisal. The committee however fails to emphasise its [thalidomide's] unlicensed status and the consequences of this for undertaking such a comparator study. Conversely the committee fails to accept the appropriateness of combining two licensed treatments (bortezomib and dexamethasone) in a manner acknowledged within bortezomib's SmPC and which has been proven to be an effective strategy in clinical trials.

1.7 The ACD suggests that the lack of standardisation [of treatment pathways] means that clinical trials are required that focus on the establishment of the position of bortezomib in the pathway of care. Bortezomib is however the now established evidence-based standard of care in patients at 1st relapse and we therefore argue that the purpose of this single technology appraisal process is to evaluate whether bortezomib is a clinically and cost-effective use of NHS resources. Detailed consideration of treatment pathways are more appropriate for NICE to consider within the clinical guideline process.

High dose dexamethasone is the only appropriate comparator for bortezomib in this appraisal

1.8 To provide further clarity around the place of bortezomib in the treatment of relapsed MM, it is also important to consider the choice of comparator in this appraisal as highlighted in section 4.3 of the ACD. As stated in paragraph 1.1, by necessity, treatment of relapsed MM needs to be individualised and patients will need access to a range of treatments throughout the course of their illness. Therefore, we believe that it is appropriate for a range of therapies, including bortezomib, to be made available if the treatment goals of achieving durable response and improved survival are to be achieved. As patients inevitably relapse, they will require access to a range of different agents during their myeloma treatment journey. Alternative treatments used in relapsed MM include repeat stem cell transplant, alkylating agents and thalidomide. It is clear from section 4.3 of the ACD that the committee particularly note that thalidomide is an agent commonly used at first relapse. Given the importance of this statement to the constitution of the draft guidance, we will address this point in some detail below, however at this point iterate two important aspects of thalidomide which have not been sufficiently considered by the committee; These are; 1. We emphasise again that thalidomide is unlicenced and therefore we are unable to conduct a comparative study as suggested by the committee. 2. Within the UK there is an increasing use of thalidomide for first line or first line maintenance treatment such that in relapsed myeloma, thalidomide is no longer a treatment option. The reasons for choosing HDD as the comparator arm in the APEX study thus becomes apparent though are dealt with later in this response.

1.9. We endorse the ERG conclusion that there are no obvious comparators other than HDD for this appraisal. However, section 4.3 of the ACD states that the committee felt that *"….lack of standardisation in the current management of MM should not preclude efforts to establish the clinical and cost-effectiveness of bortezomib within the spectrum of options used in current practice in the NHS.."* We would like the Appraisal Committee to appreciate that other treatment options were only excluded after due consideration and for sound methodological and clinical reasons. We are pleased to have the opportunity to clarify this point in the following sections. However it is important to realise that HDD is a vital component of many other treatment regimens in myeloma, eg VAD, a gold standard regimen for intensive treatment in newly diagnosed myeloma patients. Indeed the principle active component of this regimen is in fact the dexamethasone.

1.10 In the absence of comparative RCT data, it is sometimes possible to make indirect comparisons between treatments using techniques such as meta-analysis, although the validity of this approach is somewhat open to question. Also, before it can even be attempted, it is important that the internal validity and similarity of the trials being compared is carefully examined and that the findings are interpreted cautiously (Jones et al 2004). With this in mind, we iterate why HDD is the only relevant comparator below.

1.11 Thalidomide is commonly used in the treatment of relapsed MM. However, robust and meaningful comparisons of efficacy, safety and cost-effectiveness with bortezomib are not possible. We would argue that the safety, effectiveness and cost-effectiveness of thalidomide remain uncertain because the manufacturer of this product has failed to invest in proper phase III development plans. This means that thalidomide has no marketing authorisation and is not currently approved by the MHRA for any indication in the UK. In fact, there are no randomised, controlled trials evaluating thalidomide in patients with relapsed MM (Glasmacher et al, 2005). Unsurprisingly given this dearth of RCT data, the optimal dosing schedule for this product remains to be established. The limitations with the thalidomide evidence base means that indirect comparisons are simply not possible. Given all these facts, it is also obvious why thalidomide could not have been chosen as a comparator in our phase III APEX study.

1.12 If NICE were to fail to recommend the use of bortezomib, it means that patients with relapsed MM would be denied the option of using a product proven to work in this patient population in a robust RCT, but would be free to continue using an unlicensed product with efficacy unproven in adequately designed trials in this patient group. Furthermore, thalidomide is not a cheap generic treatment. Maintenance treatment acquisition costs of 50mg to 400mg doses are around £5,000 and £20,000 per year. NICE aims to deliver guidance to ensure that there is appropriate use of scarce NHS resources and yet the guidance in its current form would actually condemn NHS resources to be diverted towards a product that fails to meet any kind of modern, evidence-based medicine criteria. Perversely, NICE would be rewarding a lack of innovation and R&D investment on the part of the manufacturers of thalidomide by removing bortezomib as an option for patients.

1.13 The ACD drew attention to various other alternative treatment options and raised the suggestion that repeat stem cell transplant and anti-cancer chemotherapy are alternative treatment options. The effectiveness of repeat stem cell transplants in relapsed disease is unproven such that it would be considered to be an experimental procedure at this stage. At present this expensive procedure is rarely offered a second time in the UK and its value is currently being addressed in the context of clinical trials. Although some patients are re-exposed to previously used anti-cancer drugs such as alkylating agents, this is not a worthwhile option for many patients. Novel licensed treatment options such as bortezomib therefore fulfil an unmet medical need.

A CONCERN AROUND THE CLARITY AND DETAIL IN THE REPORTING OF THE APEX TRIAL

2.1 The ACD (section 3.5) raises concerns around the APEX trial stating that *"lack of clarity and detail in reporting the APEX RCT made the interpretation of clinical effectiveness difficult*". Ortho Biotech is concerned that in this instance, the ACD lacks balance by failing to include the ERG's final conclusion that "**these limitations do not significantly affect the overall results especially in light of clarifications received from the manufacturer."** We concur with the ERG that the APEX results are robust and that concerns over reporting of the trial were dealt with in our response to questions raised by the ERG. However, in the following sections, we provide some further information on the rationale for choosing HDD as the comparator in the APEX study, and also to clarify any remaining issues relating to the reporting and analysis of APEX.

2.2 HDD is commonly used for relapsed myeloma in clinical practice in both North America and Europe and it is considered to be an effective treatment in this setting. In the absence of an established optimal treatment for relapsed myeloma, the rationale for the selection of the comparator to VELCADE in the APEX study was based on:

Treatments available at the time the APEX study commenced (June 2002)
The treatment considered effective in clinical practice
The treatment most widely used in North America and Europe

HDD met these criteria and hence was considered by the investigators, the sponsor, the FDA and the European Regulatory Authorities to be the most appropriate comparator for the APEX study.

2.3 The ERG highlighted some apparent discrepancies between the information included in our submission and other sources such as the Richardson paper. We have fully investigated all possible discrepancies and are confident that there are no major issues that would impact the interpretation of the APEX trial. Our full set of responses to these issues are provided in Appendix 1.

CONCERNS WITH THE ECONOMIC MODEL, RESULTING IN THE CONCLUSION THAT BORTEZOMIB "HAD NOT BEEN SHOWN TO BE COST-EFFECTIVE COMPARED WITH CLINICAL PRACTICE IN THE NHS".

3.1 The ERG critique of our economic model was largely fair and balanced and we note their conclusion that ***"in general the approach taken to model disease***

progression and cost-effectiveness in this patient group seems reasonable". However, we question why this important comment, which brings a more balanced perspective to the critique, was omitted from the ACD.

3.2 We are mindful of the need to address the ERG's concerns in order to provide the Appraisal Committee with an economic evaluation that is fit for purpose. To address this, we have fully updated our original economic model and a detailed, revised report is provided in Appendix 2 of this document. The key elements that have been updated from our original submission include: a full QALY-based cost-effectiveness analysis; a detailed response to specific comments raised within the ERG report and a revised set of results incorporating all changes that were proposed as being necessary by the ERG. The key elements of this revised report are highlighted below.

3.3 In revising the economic model, we have used a two-stage approach to ensure the impact of the changes we have made are as transparent as possible. In the report in Appendix 2, we have also carefully responded to all the ERG comments and made changes to the model as appropriate. Ortho Biotech would be happy to meet with the NICE team to explain our approach in more detail if that would be helpful.

3.4 In the first set of analyses, we provide a full QALY-based analysis using the original submitted model and calculated results for the following scenarios
1st Relapse: An analysis of patients treated at 1st relapse
1st Relapse plus stopping rule: Limiting the number of cycles of bortezomib in non-responding patients
1st Relapse combination treatment: The combination of bortezomib plus dexamethasone versus HDD
1st Relapse combination plus stopping rule: The combination of bortezomib + dexamethasone and limiting the number of cycles of bortezomib in non-responding patients.

The table below presents a summary of the cost-effectiveness results for the different scenarios, with more detailed information available in Appendix 2.

Patient Group	Cost per QALY	95% CI
First relapse	£38,052	£33,629-£48,612
First relapse + stopping rule	£34,964	£30,314-£47,105
Bortezomib + Dex	£35,410	£33,293-£48,026
Bortezomib+ Dex + stopping rule	£31,764	£29,354-£47,437

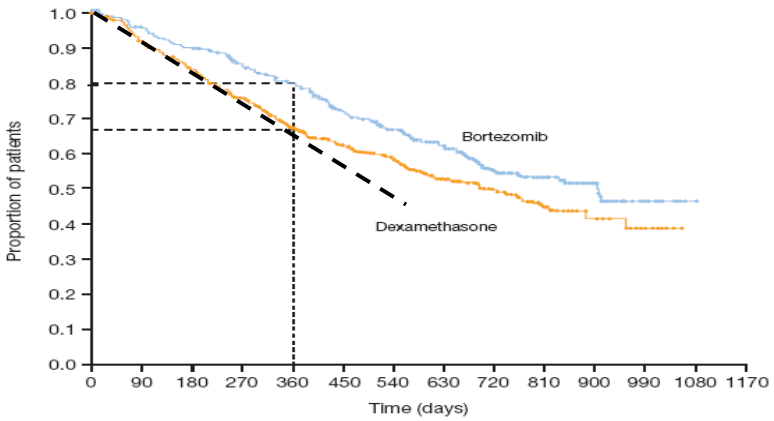
The results show that the incremental cost per QALY becomes more favourable when bortezomib is used with the stopping rule and in combination with dexamethasone. When these two strategies are employed, the cost per QALY is around £30,000.

3.5. Before presenting the results of the revised economic model, it is important to respond to the comments raised by the ERG and to describe actions we have taken to address these issues. This is described in some detail in Appendix 2. Of particular note are ERG concerns around the use of the Mayo Clinic cohort in our model (the Kumar observational study).

3.6. We agree with the ERG that Kumar is a good quality observational study and that it is the only published, credible long-term cohort data available for modelling progression in MM. The ERG state that TTP is one of the two most important drivers of cost-effectiveness in the model (cost of bortezomib being the other). It is very important to understand that the TTP and 1-year survival rates for both Bortezomib and HDD were taken directly from the randomised phase of APEX and we are therefore highly confident that these are accurate and robust parameters to use in modelling the effectiveness of HDD and bortezomib. The model is therefore driven by the APEX RCT, and the Kumar data are only used to predict post progression survival, with the same assumptions applied to both arms of the model. As a result, Kumar is not a key driver of the model.

3.7. Another key concern of the ERG was the apparent lack of HDD in the Kumar study. In fact, this is not a limitation of the model because the Kumar data are only used to model post progression survival. By definition, patients in the HDD arm would therefore have failed HDD treatment and would need to receive alternative treatments. In the model, parameter estimates of the effectiveness of HDD are taken directly from APEX.

3.8 The final major concern was whether the model overestimates survival relative to the APEX results from the Richardson et al paper. Having examined this issue, we are confident that this is not the case and that the modelled survival of 9.9 months is realistic, or even conservative. The figure below presents overall survival results at 22 months follow-up of the APEX trial (as presented by Paul Richardson at the American Society of Haematology conference in December 2005). In this analysis, the incremental survival gain for bortezomib was 6 months. However, it is important to note that in Richardson's analysis, 62% of patients (208 patients) in the HDD arm had crossed over to receive bortezomib when the study was halted prematurely on ethical grounds because of the superior benefits seen in the bortezomib arm. Therefore, the figure below is not a balanced comparison of bortezomib and HDD. Instead, it should be considered to be a comparison of bortezomib versus "HDD followed by bortezomib". To illustrate this point, the dashed line on the graph below shows the approximate rate of decline during the randomised phase. This is much steeper that the decline after the trial was halted and patients in the HDD arm were allowed to receive bortezomib. In fact, it shows exactly why it is necessary to construct a model to show the true extent of the treatment differences. It is more than reasonable for the model to predict that had patients in the HDD arm not been allowed to receive bortezomib treatment at the point of early trial termination, then the difference between bortezomib and HDD would have been greater than 6 months. Given the superior TTP and response rates observed with bortezomib, we believe that 9.9 months is likely to be a realistic, or even conservative estimate.



3.9 The revised economic model is an update of the original work provided in the manufacturer's submission. We have implemented the following improvements to our model in direct response to the ERG critique:

- We have implemented a revised analysis incorporating a more systematic approach to utility valuation in the model. We now use the utility value from the van Agthoven study (0.81) for patients in pre-progression and a value of 0.644 in post progression. This latter figure was based on the lower utility value reported by the ERG in Section 6.3.4.3, p36 of their report.
- The model cycle length is now 3-monthly for the entire time horizon of the model
- Costs of adverse events are now fully included, based on frequency and severity seen in APEX
- Cost of administration of bortezomib have been updated in line with ERG comments.
- We have revised sensitivity analysis ranges to use those suggested by ERG.
- We have considered a scenario that includes vial sharing as suggested by ERG. Market research shows that around 15% of vials are currently shared in the UK.

A summary of the updated cost-effectiveness results are presented in the table below.

Patient Group	**Cost per QALY**	**95% CI**
First relapse	£38,064	£33,236- £47,381
First relapse + stopping rule	£33,515	£28,518 – £44,135
First relapse + Bortezomib + Dex	£35,059	£33,964-£47,540
First relapse + Bortezomib + Dex + stopping rule	£30,586	£28,678-£43,717
First relapse + stopping rule + vial sharing	£30,112	£25,924 - £39,913
First relapse + bortezomib + dex + stopping rule + vial sharing	£27,566	£22,141 - £39,215

There are a number of key conclusions that can be drawn from this new set of analyses.

1. When bortezomib is used at 1st relapse and treatment is stopped in non-responders after three cycles, the incremental cost per QALY is £33,500 which is in the range that one would consider to be cost-effective.
2. Addition of dexamethsone together with a stopping rule is the most cost-effective strategy for using bortezomib, with a cost per QALY of £30,500.
3. An analysis reflecting current UK patterns of vial sharing suggests that the cost per QALY with stopping rules is around £30,000. Addition of dexamethasone to this scenario gives a cost per QALY of £27,500.
4. Given that this is a rapid, early STA, which is based on a single trial, it is our assertion that the 95% CIs give a degree of assurance that this technology is likely to be a cost-effective use of resources. None of the scenarios have upper limits that are a very large factor above the threshold and the point estimates are consistently around £30,000. Under the new STA process, which requires decision-making on the basis of early, more limited data we would argue that tighter PSA intervals are not achievable.

WHETHER YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS

4.1 In the preceding sections, we addressed issues relating to the appraisal of evidence in this submission. In addition, we would like to comment on the ACD's proposal that bortezomib should be restricted for use in *"well-designed clinical studies that focus on the establishment of the position of bortezomib in the pathway of care for people with multiple myeloma in comparison with other agents that are currently used in clinical practice in England and Wales"*. Ortho Biotech believes that this proposed recommendation is inappropriate for a number of reasons.

4.2. Firstly, as stated above, the position of bortezomib in the pathway of care was clarified in 2005 by the APEX study and therefore, further studies are not needed to establish where bortezomib can be used most effectively.

4.3 Secondly, it could be that NICE believes that the on-going MRC myeloma IX study will answer the question as to where bortezomib should be positioned, however this is not the case. Bortezomib plus dexamethasone was added to the study as an optional amendment and because it is a proven, valuable treatment for first relapse MM patients. Furthermore in this study, allocation to bortezomib treatment is not random, which is likely to limit the relevance of this study to a HTA. The study is not intended to assess either the efficacy or position of bortezomib as these questions have already been answered in the APEX trial.

SUMMARY

5.1 In conclusion, the APEX trial established bortezomib as the evidence-based standard of care for patients with relapsed MM and in doing so, clarified its appropriate place in the treatment pathway. The ACD recommendation to use

bortezomib only in clinical trials is therefore not appropriate. APEX has already successfully answered this question.

5.2. Bortezomib patients had superior response rates, increased time to progression and survival compared to HDD and the benefits were most pronounced in patients who received it at first relapse. Our revised economic analysis confirms that bortezomib is most cost-effective when used at 1st relapse and when treatment is limited to three cycles in non-responders. Combination with dexamethasone further enhances response rates and cost-effectiveness.

5.3 Ortho Biotech believes that the available evidence supports guidance recommending the use of bortezomib as a treatment option for appropriate patients at first relapse. Appropriateness can be judged by individual clinicians, but at least should include an assessment of performance status. Implementation of a stopping rule and consideration of co-administration with dexamethasone can help ensure that bortezomib treatment is a cost-effective use of scarce NHS resources.

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Appendix 1: Clarification of Issues Related to the APEX study

ERG Issues raised in Section 5.2.1	OB Response
1. There are differences in the reporting of baseline characteristics, such as the number of patients receiving more than one prior therapy. The percentages of patients receiving 2, 3 or 4 lines of therapy in the manufacturer's submission are 98%, 82%, and 34% for the bortezomib group, and 99%, 84% and 35% for the HDD group. However in the NEJM paper, 56% of bortezomib patients and 58% of HDD patients had received 2 or 3 therapies, and 4% of bortezomib patients and 7% of HDD patients had received 4 or more previous therapies	The differences in reported numbers stem from differences in definition, i.e. The NEJM reports the numbers of lines of prior therapy a patient would have received. In the Manufacturer's submission, the figures presented are taken from the unpublished APEX clinical trial report. The numbers in the manufacturers submission refer to the number of treatments received (steroids, alkylating agents, anthracyclines or thalidomide) as part of their prior lines of therapy. So, for example, a patient who received thalidomide-dexamethasone for their front-line therapy would have received 2 of those drugs. This is different to the number of lines of therapy a patient would have received.
2. There are other small differences between the baseline characteristics in the NEJM paper[4] and in the manufacturer's submission (Table 7, p.33). Karnofsky Performance Scale (KPS) scores ≥ 70 are reported in the NEJM paper, whereas KPS scores ≥ 60 and ≥ 80 are reported in the manufacturer's submission. However, the manufacturer's submission's KPS ≥ 60 figures are the same as the NEJM KPS ≥ 70 ones. It is not clear where the manufacturer's submission's KPS ≥ 80 figures come from as these aren't in the NEJM paper. These figures are not reported for the whole ITT population, and use n=322 and n=325 for bortezomib and HDD, respectively.	The figures in the manufacturer's submission are taken from the unpublished APEX trial report. However, as pointed out in the ERG, there is an error in the figures. The values included in the submission for KPS ≥ 60 are actually the value for KPS ≥ 70. The values for KPS ≥ 60 should read 321 (99%) for VELCADE, 324 (99%) for dexamethasone and 645 (99%) for Total.
3. Serum β_2-microglobulin levels are reported as medians in the NEJM paper, but the manufacturer's submission presents these as β_2M>2.5 and β_2M>5.5. It is not clear where this data comes from. CrCl ≤ 20 is presented in the NEJM paper whereas CrCl ≤ 60 is shown in the manufacturer's submission. These figures are quite different (8/330 and 5/323 in the NEJM paper, 110 and 111 in the	The figures for both serum β_2-microglobulin levels and creatinine clearance are taken from the unpublished APEX clinical trial report.

manufacturer's submission).	
4. Statements in the manufacturer's submission regarding response to therapy (n=627, not ITT) reflect data in the NEJM paper (and in abstracts for later results) although no information was found in the NEJM paper[4] regarding durability of responses.	The information in the manufacturer's submission was taken from the unpublished APEX clinical trial report and was converted from days to months. The median duration of response for the original and updated APEX analyses were reported in the updated APEX poster (presented at ASH 2005).
5. Grade 3 adverse events were reported in 61% of patients receiving bortezomib and in 44% of patients receiving dexamethasone. Both the manufacturer's submission and the NEJM state this, but the manufacturer's submission does not include the significant p values stated in the NEJM paper ($p<0.01$).	We can confirm that the P value <0.01 applies to the data presented as part of the Manufacturer's submission.
6. Hazard ratios were presented for key outcome measures, but it was not possible to check these as insufficient data were reported. For example, in Table 10 (p.49), HDD results are reported as 'non evaluable', yet a hazard ratio and p value for treatment difference are reported.	In Table 10 of our submission, it reports 'non evaluable' for the HDD results. This is a result of the median survival not being reached at the median follow-up of 8.3 months. We were able to report a p-value for treatment difference because the difference in hazards between the two treatment arms utilizes all the survival information, and could be estimated irrespective of the median survival being reached.
7. Due to the early termination of the APEX trial a high level of censoring was applied to TTP and survival data, and it is not clear what impact this as well as the high rate of attrition will have on outcomes. Also, it is not known how the high rate of crossovers from HDD to Bortezomib affected results; it may be that the effect of crossovers was to reduce the difference in effectiveness between the two groups but lack of clarity regarding statistical analysis hinders this conclusion.	It is correct that there a high level of censoring was applied to the TTP and survival data. However, we would point out that most of the censoring was due to study cutoff with small number of patients lost to follow-up. Please see further explanation below.

Further detail for point 7

Of the 534 censored cases, most of them (384 in total: 216 in the VELCADE arm, 168 in the dexamethasone arm), were censored at the data cutoff for overall survival, 13JAN2004. The other 150 cases were censored prior to the data cutoff. (Table 1).

Table 1. Distribution of Events and Censoring for Overall Survival: Censoring Prior to Cutoff Considered as LTFU
(Study M34101-039, Intent-to-Treat Population)

Survival Outcome	VELCADE (N=333)	Dexamethasone (N=336)
Died, n (%)	51 (15)	84 (25)
Censored, n (%)	282 (85)	252 (75)
Due to data cutoff	216 (65)	168 (50)
Loss to follow-up (a)	66 (20)	84 (25)

Note:
a) A subject was considered as lost to follow-up if the censoring date was before the survival data cutoff, 13JAN2004.

To assess the impact of the 582 patients censored cases on the analysis of overall survival, sensitivity analyses were undertaken:

1) For any subjects who were censored prior to the survival data cutoff (13JAN2004), termed as lost-to-follow-up (LTFUs) in the following tables, impute the survival data as censored cases at the cutoff.
2) Impute those LTFUs as events (i.e., deaths) at the survival data cutoff.

Overall survival was then analyzed using the imputed data. The hazards ratio estimate, and its 95% confidence internal were presented in Table 2, along with the p-value based on log-rank tests.

Table 2. Sensitivity Analyses of Overall Survival: Censoring Prior to Cutoff Considered as LTFU
(Study M34101-039, Intent-to-Treat Population)

Imputation for LTFU (a)	Hazards Ratio (95%CI) (b)	P-value (c)
No imputation	0.5676 (0.3997, 0.8059)	0.0013
Imputed by censoring at cutoff	0.5725 (0.4040, 0.8111)	0.0015
Imputed by event at cutoff	0.6444 (0.5078, 0.8177)	0.0003

Note:
a) A subject was considered as lost to follow-up if the censoring date was before the survival cutoff, 13JAN2004.
b) Hazards ratio was estimated by a univariate Cox model stratified by stratification factors.
c) P-value was based on a logrank test stratified by stratification factors.

According to the study design, survival was evaluated every 3 months during long-term follow-up; therefore, an alternative approach was taken to address the question, in which patients known to be alive within 90 days prior to the survival data cutoff were considered censored due to data cutoff, and were not considered lost to follow-up. Patients who were not known to be dead, but whose last follow-up was more than 90 days prior to the study cutoff were considered lost to follow-up. As a result, only 17 subjects (11 patients in the VELCADE group and 6 in the dexamethasone group) were considered as LTFUs (Table 3).

Table 3. Distribution of Events and Censoring for Overall Survival: Censoring >90 Days Prior to Cutoff Considered as LTFU
(Study M34101-039, Intent-to-Treat Population)

Survival Outcome	VELCADE (N=333)	Dexamethasone (N=336)
Died, n (%)	51 (15)	84 (25)
Censored, n (%)	282 (85)	252 (75)
Due to data cutoff	271 (81)	246 (73)
Loss to follow-up (a)	11 (3)	6 (2)

Note:
a) A subject was considered as lost to follow-up if the censoring date was more than 90 days prior to the survival data cutoff, 13JAN2004.

The same imputation methods as explained above were employed. The ensuing hazards ratio estimate, its 95% confidence internal, and the p-value were presented in Table 4.

Table 4. Sensitivity Analyses of Overall Survival: Censoring >90 Days Prior to Cutoff Considered as LTFU
(Study M34101-039, Intent-to-Treat Population)

Imputation for LTFU (a)	Hazards Ratio (95%CI) (b)	P-value (c)
No imputation	0.5676 (0.3997, 0.8059)	0.0013
Imputed by censoring at cutoff	0.5641 (0.3979, 0.7996)	0.0013
Imputed by event at cutoff	0.6271 (0.4531, 0.8679)	0.0045

Note:
a) A subject was considered as loss to follow-up if the censoring date was more than 90 days prior to the survival data cutoff, 13JAN2004.
b) Hazards ratio was estimated by a univariate Cox model stratified by stratification factors.
c) P-value was based on a logrank test stratified by stratification factors.

As seen from the results above, the estimates of hazards ratios remained consistent with the original analyses results in all sensitivity analyses performed. The p-values also remained highly significant in all these analyses.

Appendix 2: Revised Economic Report

(Attached)

Appendix 2: Revised Economic Report

Overall, Ortho Biotech believes that the ERG critique of our economic model was fair and balanced. We note the ERG conclusion that "in general the approach taken to model disease progression and cost effectiveness in this patient group seems reasonable". The ERG does raise some specific areas in our economic model, which are apparent causes for concern. We are mindful of the importance of thoroughly addressing ERG concerns in order to provide the Appraisal Committee with an economic evaluation that is fit for purpose.

As a result we have updated our original economic modelling approach to include the use of QALYs as our effectiveness measure instead of life years gained, provided a detailed response to specific comments raised within the ERG report and revised our economic model in line with the ERG proposals.

In updating the economic model, we have taken a two-stage approach to ensure transparency and to help understand the importance of changes made to the overall results. In the section entitled "Update to Submitted Model" we provide a full QALY-based analysis using our original submitted model. In this set of analyses, we have input a utility value of 0.81 into the original model and have also changed the cost of "other care" from £443 to £478 per month in line with the ERG's comment that we had under-inflated this parameter in our original model, submitted in February 2006. All other modelling assumptions remain constant.

In the second set of analyses, entitled "Revised Model". We run a new cost utility analysis incorporating the full set of changes that have been driven by the ERG critique.

1. Update to Submitted Model

In this scenario, we have updated our original economic model to calculate incremental cost per QALY values for all analyses that were presented as part of original submission to NICE. We have not made any changes to the model structure or parameters other than update utility values and cost of other care. The analyses we have undertaken are as follows:

- 1st Relapse: An analysis of patients treated at 1st relapse
- 1st Relapse plus stopping rule: Limiting the number of cycles of bortezomib in non-responding patients
- 1st Relapse combination treatment: The combination of bortezomib plus dexamethasone versus HDD
- 1st Relapse combination plus stopping rule: The combination of bortezomib + dexamethasone and limiting the number of cycles of bortezomib in non-responding patients.

The results of these analyses are presented below.

1.1 First Relapse

For ease of reference, in this table we present the results that were submitted as part of our response to ERG questions in April 2006.

Table 1: Cost Effectiveness Results of First Relapsed Patients

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	35.8	24.5	11.2
Mean discounted overall survival	32.5	22.6	9.9
% Alive			
1 year	87%	72%	15%
2 years	65%	45%	20%
5 years	23%	12%	11%
QALYs, months	26.35	18.33	8.0
Costs			
Velcade and/or HDD	£21,035	£82	£20,953
Other care	£15,532	£10,808	£4,724
Total	£36,566	£10,890	£25,677
Cost per discounted LYG			£31,146
Per QALY gained			£38,452

1.2 First Relapse plus Stopping Rule

An explanation of the method used to undertake this analysis can be found in Section 3.7.4.1, p84 of our original manufacturer submission. Model sensitivity analyses demonstrate that cost-effectiveness is optimal when bortezomib treatment is stopped in non-responders after 3 cycles. The results shown in Table 2 indicate that use of this stopping rule decreases the mean acquisition costs of bortezomib by around £6,252 (£21,860 to £15,608). The cost per QALY falls from £38,452 to £34, 964.

Table 2: Cost effectiveness Results First Relapse plus Stopping Rules

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	34.0	24.5	9.4
Mean discounted overall survival	30.9	22.6	8.2
% Alive			
1 year	79%	72%	7%
2 years	61%	45%	16%
5 years	22%	12%	10%
QALYs, months	25.01	18.33	6.7
Costs			
Velcade and/or HDD	£15,608	£82	£15,526
Other care	£14,746	£10,808	£3,938
Total	£30,354	£10,890	£19,464
Cost per discounted LYG			£28,321
Per QALY gained			£34,964

1.3 First Relapse Combination Treatment

An explanation of the method used to undertake this analysis can be found in Section 3.7.4.3, p86 of our original submission. Table 3 below presents the results of these analyses.

Table 3: Cost effectiveness results of 1st Relapse Combination Treatment

Outcomes	Velcade + HDD	HDD	Difference Velcade+HDD v HDD
Mean overall survival, months	37.0	24.5	12.5
Mean discounted overall survival	33.6	22.6	11.0
% Alive			
1 year	87%	72%	15%
2 years	68%	45%	22%
5 years	24%	12%	12%
QALYs, months	27.24	18.33	8.9
Costs			
Velcade and/or HDD	£21,117	£82	£21,035
Other care	£16,060	£10,808	£5,252
Total	£37,176	£10,890	£26,286
Cost per discounted LYG			£28,682
Per QALY gained			£35,410

The mean incremental OS increases from 9.9 months to 11.0 months for bortezomib plus dexamethasone versus HDD. The incremental costs associated with bortezomib plus dexamethasone is increased marginally by £571. The resultant cost per QALY is £35,410.

1.4 First Relapse Combination plus Stopping Rule

The ERG in their report present the results of a scenario analysis which combines the addition of bortezomib plus dexamethasone and limiting the number of cycles of bortezomib treatment in non-responding patients across a patient group that varies by staging of disease. The results of the ERG analysis show that it is most cost effective using this strategy in the first relapse setting and so we have also incorporated this analysis into our economic model. The results of the analysis are presented below.

Table 4: Cost Effectiveness Results of First Relapse Combination plus Stopping Rule

Outcomes	Velcade + HDD	HDD	Difference Velcade+HDD v HDD
Mean overall survival, months	35.2	24.5	10.7
Mean discounted overall survival			
Total	32.0	22.6	9.4
% Alive			
1 year	79%	72%	7%
2 years	64%	45%	19%
5 years	23%	12%	11%
QALYs, months	25.91	18.33	7.6
Costs			
Velcade and/or HDD	£15,668	£82	£15,586
Other care	£15,274	£10,808	£4,466
Total	£30,943	£10,890	£20,053
Cost per discounted LYG			£25,729
Per QALY gained			£31,764

The resultant cost per QALY decreases to £31,764 confirming that this is the most cost effective treatment strategy from the four treatment scenarios considered in our original model.

1.5 Results of Sensitivity Analysis

We have rerun probabilistic sensitivity analyses for all the scenarios considered in the submitted model (see Table below). We have not changed the parameter ranges. Please see our letter submitted to NICE in April 12th 2006 in response to the SHTAC questions for further explanation of the ranges we have used in this analysis.

Table 5: Probabilistic Sensitivity Analysis Results (Ravinder to provide)

Patient Group	Cost per QALY	95% CI
First relapse	£38,052	£33,629-£48,612
First relapse + stopping rule	£34,964	£30,314-£47,105
First relapse + bortezomib	£35,410	£33,293-£48,026

+ Dex		
First relapse + bortezomib + Dex + stopping rule	£31,764	£29,354-£47,437

The results of the probabilistic sensitivity analysis show that the most favourable cost effective treatment strategy is the combination of bortezomib plus dexamethasone and stopping bortezomib treatment at cycle three in non-responding patients. The 5th percentile is £29,354 and the 95th percentile is £47,437.

2. Clarification of ERG comments on economic evaluation

The structured ERG critique of our model was very helpful in laying out those areas of our economic evaluation that required further clarification. We have addressed and grouped the ERG's concerns under the following headings:

- Modelling approach/Model structure
- Structural Assumptions
- Clinical Effectiveness
- Patient Outcomes HRQL
- Resource use
- External consistency
- Assessment of uncertainty

2.1 Modelling Approach/Model Structure

2.1.1 In section 6.3.3.1, the ERG state "Given that the time to relapse (between different regimens) may be an important factor in the prognosis of disease a 1-year cycle may not be appropriate, and the use of a 3-month or 6-month cycle throughout the time horizon may reflect a better profile of disease over time. A half-cycle correction has not been used"

In our original model we used quarterly cycles from 0-3, 4-6 months, then six monthly from months 7-12, and then annual cycles for the remaining time horizon of the model.

We structured the model in this manner on the basis of the APEX data, which showed median time to progression of 6.2 months in the bortezomib arm and 3.49 months in the HDD arm. Following progression, the model considered the remaining survival time until death and we felt that this was adequately captured by the annual cycle length data.

However, we have adjusted the cycle length accordingly to the ERG's recommendation and now use quarterly cycles throughout the model. This is included within the revised version of our economic model.

2.2 Structural Assumptions

2.2.1 In Section 6.3.3.2, the ERG state "Whilst Kumar et al study seems a good quality observational study, and there is an absence of alternative data sources available, when applying this data in the context of the CEA presented there may be some areas of uncertainty."

We agree with the ERG that Kumar is a good quality observational study and that this is the only published, credible long-term cohort data available for modelling progression in MM.

As stated in the ERG report, TTP is one of the two most important drivers of cost-effectiveness in the model (cost of bortezomib being the other). It is very important to understand that the TTP and 1-year survival rates for both Bortezomib and HDD were taken directly from the randomised phase of APEX and we are therefore highly confident that these are accurate and robust parameters to use in modelling the effectiveness of HDD and Bortezomib.

The early termination of the APEX trial, however does affect the ability to model long-term outcomes and mortality data with bortezomib and dexamethasone. The Kumar data was used for two reasons within our economic model. The first was to model the long-term **post progression** survival for both bortezomib and dexamethasone, and the second was to validate and calibrate the model in terms of overall mortality. For further details of the steps involved in the validation and calibration of the model, please see our response to question B2 of our letter submitted to NICE in April 12th 2006.

To clarify, the model, is mainly driven by the APEX RCT. The Kumar data are only used to predict post progression survival, with the same post progression assumptions being applied to both arms of the model.

We have reviewed all the comments raised by the ERG relating to the use of the Kumar study and present a detailed response to each of their specific questions below.

2.2.1.1 A subset of the Mayo patient data presented

From an economic modelling perspective, we were interested in utilising the long-term clinical data from all patients with relapsed multiple myeloma from the Kumar et al study as this represented the population that was the most similar to that of the APEX trial. Therefore we used the data from all 355 patients who had received a second treatment to understand the impact of relapsed multiple myeloma.

2.2.1.2 This observational study reports data collected over a 13-year period (in a USA context), and patients may not have benefited from the latest treatment protocols

In table 4, p 873 of the Kumar et al published paper, it summarises the types of therapies by line of regimen administered to patients within this study. The therapies used in this patient cohort are reflective of those that would be used in the UK, although we accept that the patterns of usage by line of therapy may not entirely reflect current UK practice. At the time of this study, clinicians were beginning to use Thalidomide in multiple myeloma, but its use may be under-represented. As thalidomide is now moving increasingly to front-line treatment, the implications of this are probably not important. It is very important to understand that this study represents the best available data on the natural history of relapsed disease in an unselected group of patients that and the median survival of 17.1 months from first relapse is in line with other reported studies (Pandit et al 2001). Again we would reemphasise that we have applied this estimate equally to both the bortezomib and dexamethasone arm to estimate long-term survival following progression within our economic model.

2.2.1.3 HDD was not one of the reported treatment regimens for the observational study

The lack of HDD in the Kumar study is not an important limitation of this study because this data is only used to model post progression survival. By definition, patients in the HDD arm would have failed HDD treatment and would need to receive alternative treatments. However, we would also like to point out that in fact patients did receive dexamethasone in the Kumar paper. Table 4, p873 of the Kumar study shows therapy by line of regimen and it is evident from this information that dexamethasone as a key component of the VAD regimen was the third largest therapy used.

2.2.1.4 The observational data are not specific on which patients had what treatment and when

We accept that we were not able to access patient level data but table 4 does provide a summary of treatment regimens by line of therapy.

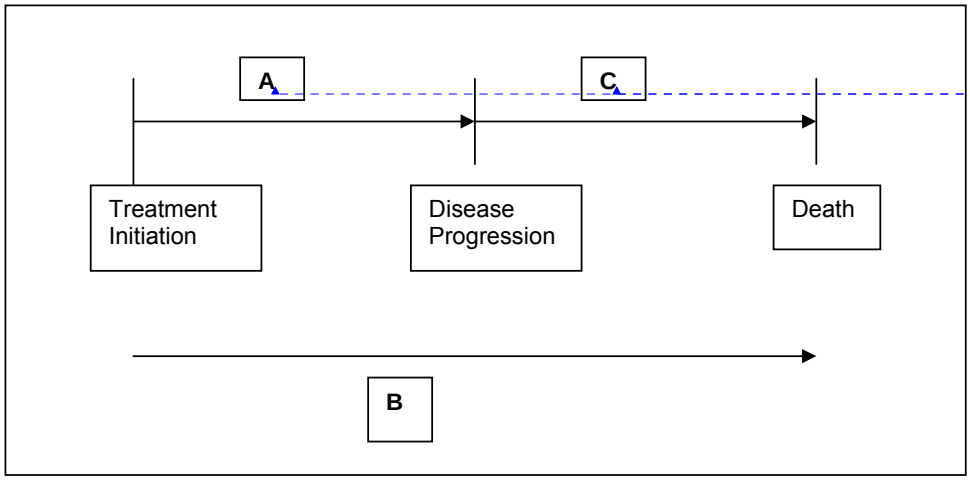
It is also important to note that section 6.3.3.2 of the ERG concludes of the Kumar data that "in the absence of alternative published data on the long-term survival benefits of MM that this is the best data source available". Again we would reiterate that these data are only used in the economic model to estimate the post progression survival time and that the same data is used for both treatment arms.

2.2.2 In Section 6.3.3.2 it states, "The manufacturer's submission assumes that there are independent benefits for TTP and OS. Given the workings of the model these benefits may not be independent, and it may be that the group of patients who have OS benefits will also have TTP benefits. Thus there may be some double-counting for the effect of bortezomib. The submission states this not to be the case, but the ERG would like further clarification of this".

The model is split into two time periods otherwise known as partitions. The first partition considers the time from initiation of treatment until disease progression, relapse, or death from any cause and the second considers those patients who are still alive and have progressed until their death.

Among patients who are alive at the point of progression time until death is estimated as the difference in overall survival and time to progression. This is illustrated in figure 1 below.

Figure 1: Schemata of Survival Estimation within the Economic Model



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The hazard ratio for TTP (e.g. labelled as A) determines the difference between treatments in time within the first partition. The hazard ratio for overall survival (OS labelled as B) determines the difference between treatments in overall survival.

Therefore, the difference between B and A (i.e. B minus A) gives us the difference between two treatment arms in the time period after progression to death (labelled as C). In essence C=B-A and hence C and A are not dependent and not duplicated.

In order to illustrate this, we present below an example of the transit probabilities taken from our original model (See Appendix 13 of our original submission).

Table 6 below shows the percentages of patients who died on regimen, switched to another regimen, or stayed on regimen for bortezomib.

Table 6: Example of transit probabilities taken from our original economic model

End month	Regimen	Number of patients in each state by period, starting cohort of 100 patients				Percent of patients since start in each state by period		
		Died on regimen	Switched to another regimen	Stayed on regimen	Total alive	Died on regimen	Switched to next regimen	Stayed on regimen
3								
	1	11	10	79	100	4%	6%	91%
	2	10	16	74	100	3%	8%	88%
	3	16	16	68	100	5%	20%	75%
	4	19	20	61	100	6%	25%	69%
	5	22	22	56	100	7%	27%	65%
	6	18	27	55	100	6%	30%	64%

When the percent of patients who died is changed, the percent of patients who switched to another regimen (next to last column) also change. This occurs because the sum of the last 3 columns must equal 1. By decreasing the percent of patients who died, the model increases the percent of patients who switched regimens (as shown in above Table 6).

Table 6 illustrates how use of both the TTP and OS hazard ratios are not equivalent to double-counting the effect of bortezomib. The former indicates how long the patient stays on regimen 2. The latter indicates -- given the patient no longer stayed on regimen 2 -- whether the patient died or switched to another regimen.

2.2.3 In Section 6.3.3.2 it states, "The model assumes that there is an overall survival hazard ratio of 0.42 (from APEX RCT) in the first year and 0.83 in years 2 and 3. The latter ratio has not been justified".

It is correct that the overall survival hazard ratio of 0.42 is taken from the APEX trial in the first year. The model calibrates the value of 0.83 in years 2 and 3 based on the Kumar data. More specifically, we use the transit probabilities from Kumar data (table 3 of Kumar study) and then we apply the first year hazard ratios. In the next step an adjustment is made to reconstruct the survival curve in the APEX trial. In order to make the adjustment the model constructed with Kumar transit probabilities is calibrated to calculate year 2 and 3 hazard ratios.

2. 3 Clinical Effectiveness

Also in Section 6.3.4.2 it states, "In the model the treatment effect is assumed to last for three years in the model, and the ERG consider that this has not been justified sufficiently in the report".

The duration of treatment effect for bortezomib used within our economic model was based on the published results from the 22-month follow-up analysis of the APEX trial. At 22-months follow-up the median overall survival for bortezomib was 29.8 months, which equates to approximately 2.5 years. In the revised economic model we have rerun the sensitivity analysis and report the results in section 3.

2.4 Patient outcomes - HRQL

In Section 6.3.4.3, the ERG state, "the submission presents an argument for not using the EQ5D in this patient group, however, this argument is not generalisable to use of HRQL per se, especially as the submission itself highlights the negative impact of MM on the quality-of-life of this patient group".

We believe that life-years gained are an appropriate endpoint, but we acknowledge NICE's desire for cost per QALYs. We have addressed this point fully and the revised model now uses QALYs rather than life-years gained.

The ERG in Section 6.3.4.3 of their report present the results of their own literature review of health state values for the MM patient group. We note that they have identified the Van Agthoven et al 2004 and Gulbrandsen et al 2001 clinical papers that we

previously identified as part of our response to ERG questions in April 2006. A summary of these studies is presented in Table 7 below.

Table 7: Summary of the identified utility studies in MM

Study feature	Study	
	Gulbrandsen et al 2001	van Agthoven et al 2004
Country, N	Scandinavia N = 344	Netherlands N=261
Disease status	Newly diagnosed, symptomatic	Newly diagnosed, symptomatic
Patient demographics	Age: median 51/54 years Gender: 65%/56% male	Age: median 55/56 years Gender: 57%/61%
Study design	Multicentre non-randomised trial with matched control group	Multicentre RCT
Treatments, n	HDT/SCT, n = 274 Oral MP, n = 70 [a]	Intensive chemo, n =129 HDT/SCT, n = 132
Health value methodology(s)	EORTC QLQ-C30 mapped to 15-D	EuroQol Index
Reporting of utilities	6 months	6, 12, 18 and 24 months
Utilities available for multiple myeloma disease stages	No	Yes, for responders. Assumptions made to obtain utility of 0.644 for non-responders
Utility values	15-D HDM/SCT 0.7334 MP 0.7896	EuroQol for responders 6m Chemo 0.81 HDT/SCT 0.65 12m Chemo 0.80 HDT/SCT 0.62 18m Chemo 0.81 HDT/SCT 0.69 24m Chemo 0.77 HDT/SCT 0.75

RCT = randomised controlled trial, MP = oral melphalan and prednisone, HDM/SCT = high dose melphalan and stem cell transplant, αINF = subcutaneous interferon α2b, EuroQol Index = time trade off values, IHQL = Index of Health-Related Quality of Life (uses standard gamble values), 15-D = 15 dimensional scale using rating scale values, m = months, NR = not reported.

The ERG suggests from their review of these two studies that the health state value in patients with MM may range between 0.644 and 0.789. They also identify a health state

valuation study, Kind et al 1998, which elicited utility values using the EQ5D from the age group 60-69 years within the general population. The study reports a health state utility value in the range 0.806-0.829. "The ERG concludes that *health state values for those with MM may be expected to be somewhat lower*." We disagree that people in a plateau phase of this condition would be expected to have lower utility values for reasons we explained in our original submission and because of the phenomenon of adaptation, however, we acknowledge that lower values could be expected post progression and we address this issue below.

In April when we updated our model to provide the ERG with a cost per QALY estimate, we applied the utility estimate of 0.81 based on the results obtained from the responder group at 18 months from the van Agthoven study to the estimated survival difference. This value was felt to reflect the health state utility at first relapse. More importantly, this value was considered to be the most relevant to this appraisal because it was the only one of the published studies that reported utility values according to responder rate (an important consideration in our modelling work) and because it used a direct valuation technique rather than a less well accepted, indirect mapping exercise.

In light of the ERG's comments, we have revised our utility estimates within our economic model to include different utility estimates for the pre and post-progression phase of the model and have applied these estimates to the individual mean survival results for bortezomib and HDD. In the pre-progression phase we used the utility value of 0.81 taken from the Agthoven study, and in the post-progression phase we used the utility value of 0.644. The estimate of 0.644 was based on the utility score for non-responders reported in the Agthoven study, which is the most conservative estimate from this study. We believe that this new approach, which has been implemented in light of the ERG review, provides a much more robust approach to the evaluation of QALYs in the model.

In addition, the impact of the chosen baseline utility estimates on the cost per QALY has been tested within sensitivity analysis. Please see the results in the revised economic model section 3 below in Table 14.

2.5 Resource use

2.5.1 In Section 6.3.4.4 it reports, "The manufacturer's submission estimates an administration cost per dose of £79, with a mean total administration cost of £1,672 per patient. The ERG considers this may be an underestimate of the actual resource use and cost for the administration of each dose of bortezomib".

The ERG suggest that when it is assumed that bortezomib is administered in an outpatient setting, each dose of bortezomib is likely to involve an outpatient visit in the range of £86 to £93, in addition to pharmacy preparation time in the range of £20-£25. The sum of the outpatient and pharmacy time per dose of treatment may be in excess of £100.

We have reviewed the ERG 's comments and have revised cost of administration associated with bortezomib treatment in our revised model accordingly. Specifically, we have increased the cost of administration to £112 per dose of treatment. This is based

on the sum of the mid point of the range of cost of clinic visit (£90) and the mid point of the range of the cost of pharmacy preparation time (£22.50) suggested by the ERG.

2.5.2 Section 6.3.4.4 also states, "The manufacturer's submission does not address the issue of additional resource use attributable to adverse events which may be more frequent with the use of bortezomib, compared to HDD".

The ERG acknowledges the inclusion within our original submission of a sensitivity analysis, which considered the impact of the cost of adverse events by increasing 'other costs' by 25% in the bortezomib treatment group. This increased, the cost from £443 to £554 per month. However, they point out that where serious adverse events occur with treatment there may be significant costs, which have, not be addressed in our original submission.

Based on these comments we have now formally incorporated costs of adverse events in the revised economic model for bortezomib and HDD treatment. Table 8 below summarises the data that was included in this calculation.

Table 8: Cost of Adverse Events

		Incidence		Cost (GBP 2006)	
Severe Adverse Event	Cost per event (GBP 2006)	Velcade	HDD	Velcade	HDD
Anaemia	3,228	10.0%	11.0%	323	355
Thrombocytopenia	1,653	30.0%	6.0%	496	99
Neutropenia	3,854	14.0%	1.0%	540	39
Others	501	21.0%	42.0%	105	210
	Totals	75.0%	60.0%	1,463	703

Sources: Richardson, NEJM, 2005(Table 3 on page 2495). Wake et al. Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation. Health Tech Assessment 2002; 6:3. Available for downloading free of charge for personal use from the HTA website (http://www.ncchta.org).

Inflation from 2002 to 2006 is 13.5%

In the updated model we have included costs for grade 3 or 4 adverse events that were reported within the APEX RCT. These included four key categories: anaemia, thrombocytopenia, neutropenia and all other listed grade 3 or 4 such as nausea and vomiting. We applied UK costs to these events based on data taken from the health technology assessment report for rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma by Wake et al in 2002 and we inflated these costs to current values. The results of this analysis show that the cost of adverse events associated with bortezomib is £1,463 and £703 for HDD.

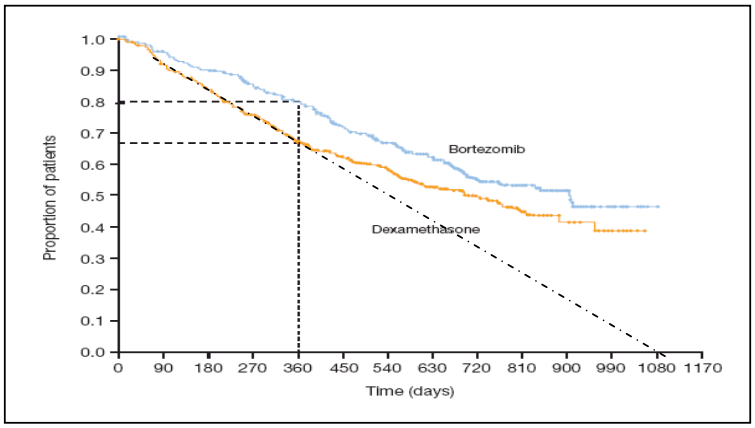
We have also included this parameter estimate within the revised sensitivity analysis (see Table 14).

2.6 External consistency

In Section 6.4.2 it states, "After the first year, the model overestimates patient survival in the treatment arm. Furthermore the treatment effect is also higher than shown in the trial by roughly 40% over the two years. The ERG considers that the model may overestimate the treatment effect of bortezomib".

We disagree with the ERG's statement that the model overestimates the treatment effect for bortezomib. The economic model predicts an incremental survival benefit of 9.9 months for bortezomib based on a lifetime analysis. When we compare this with the published incremental survival gain from APEX of 6 months (presented by Paul Richardson at the American Society of Haematology conference in December 2005 (ASH) (Please see figure below)), it is clear that the results from the economic analysis do not represent an overestimation. Figure 2 below presents the overall survival results of bortezomib compared to HDD at 22 months follow-up of the APEX trial. It is important to note that in this analysis 62% of patients (208 patients) in the HDD crossed over to bortezomib when the study was halted prematurely on ethical grounds because of the superior benefits seen in the bortezomib arm. Therefore, the comparison presented in figure 2 is not a balanced comparison of bortezomib and HDD and should be considered as being bortezomib versus HDD followed by bortezomib. As an illustration the dashed line on the graph below shows the approximate rate of decline during the randomised phase. This is much steeper that the decline after the trial was halted and patients in the HDD arm were allowed to receive dexamethsone. This is exactly the reason why it is necessary to construct a model to show the true extent of the treatment differences. It is intuitively sensible for the model to show that had HDD patients not been allowed to receive bortezomib at the point of early trial termination, then the difference between bortezomib and HDD would have been greater than 6 months. Given the superior TTP and response rates observed with bortezomib we believe that 9.9 months is likely to be a realistic, or even conservative estimate.

Figure 2: APEX Survival results at 22-month follow-up



--------- Survival curve if HDD patients had not crossed to bortezomib

2.7 Assessment of uncertainty

In section 6.5.5 the ERG state, " similar to the one way sensitivity analysis, the ERG considers the ranges used for the PSA to be inappropriate (e.g. where possible ranges should be related to the confidence intervals of the data)"."

Determining the appropriate ranges for key parameter estimates within an economic model relies on a certain level of pragmatism in the absence of data to inform these

analyses. We have reviewed the ERG's comments and have revised our sensitivity and PSA ranges to reflect those considered by the ERG in their amended analyses. These have been included within our revised economic model.

3. Revised Economic Model

As described above, we have revised our submitted economic model to incorporate the following changes:

- Adjusted the utility value pre progression to 0.81
- Adjusted the utility value post progression to 0.644
- Adjusted the cycle length (3-monthly cycles for the entire time horizon of the model)
- Cost of adverse events
- Cost of administration of bortezomib.
- Revised sensitivity analysis ranges

The model structure, methods and all other parameter estimates considered within the economic model remain unchanged. Table 9 presents a summary of the key parameters that have been changed, ranges used in sensitivity analyses and data sources considered within the model.

Table 9: Key parameters, ranges in sensitivity analyses and data sources used in the model

Parameters	Bortezomib	HDD	Range	Data source
Utilities Pre-progression	0.81	0.81	+/- 10%	Agthoven et al 2004
Utilities Post-progression	0.644	0.644	+/- 25%	Agthoven et al 2004
Duration of treatment effect (years)	3	3	2-4	Based on updated survival data from APEX. Richardson et al 2005
Hazard Ratio - TTP	0.56		0.44-0.71	Table 9 ERG report
Hazard Ratio - OS	0.42		0.30-0.59	Table 9 ERG report
Cost per course*	£21,080	£82	+/- 25%	Table 9 ERG report
Cost of other care	£478	£478	+/- 25%	Table 9 ERG report
Cost of adverse events	£1463	£702	+/- 25%	Table 9 ERG report

* Please note we have increased the administration cost associated with the administration of bortezomib

3.1 Cost Effectiveness Results

Within this section we present the results of the revised economic model. Simple one-way and probabilistic analyses are also presented for each analysis undertaken.

3.1.1 Revised Model

The results of the first relapse analysis show that the incremental cost per QALY of bortezomib at first relapse compared to HDD is £38,064, compared to £38,452 used in the original model. These results are very close to the figures presented in section 1 that used the structural assumptions used in our original submitted model. This shows that the ERG's proposed structural changes to our model do not impact the results to any significant degree.

Table 10: Cost effectiveness results of patients at first relapse

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	37.3	25.8	11.5
Mean discounted overall survival	34.0	23.9	10.1
% Alive			
1 year	87%	72%	15%
2 years	65%	45%	20%
5 years	23%	12%	11%
QALYs, months	26.08	17.47	8.6
Costs			
Velcade and/or HDD	£21,860	£82	£21,778
Other care	£15,592	£10,808	£4,784
Adverse events	£1,463	£703	£760
Total	£38,914	£11,593	£27,322
Cost per discounted LYG			£32,452
Per QALY gained			£38,064

3.1.2 Updated analyses

Three updated analyses have been considered within the revised model:

- 1st Relapse plus stopping rule: Limiting the number of cycles of bortezomib in non-responding patients
- 1st Relapse combination treatment: The combination of bortezomib plus dexamethasone after versus HDD
- 1st Relapse combination plus stopping rule: The combination of bortezomib + dexamethasone and limiting the number of cycles of bortezomib in non-responding patients.

3.1.2.1 First Relapse plus stopping rule

Using a stopping rule, limiting bortezomib treatment for non-responders to three cycles decreases the cost per QALY by around £4,549 to around £33,000.

Table 11: Cost effectiveness results of 1st Relapse plus Stopping Rules

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	35.5	25.8	9.7
Mean discounted overall survival	32.4	23.9	8.5
% Alive			
1 year	79%	72%	7%
2 years	61%	45%	16%
5 years	22%	12%	10%
QALYs, months	24.95	17.47	7.5
Costs			
Velcade and/or HDD	£16,220	£82	£16,138
Other care	£14,806	£10,808	£3,998
Adverse events	£1,463	£703	£760
Total	£32,489	£11,593	£20,896
Cost per discounted LYG			£29,649
Per QALY gained			£33,515

3.1.2.2 First Relapse combination treatment:

The results of this analysis show that the combination of bortezomib with dexamethasone results in a cost per QALY of £35,059.

Table 12: Cost effectiveness results of 1st Relapse plus Combination Treatment

Outcomes	Velcade + HDD	HDD	Difference Velcade+HDD v HDD
Mean overall survival, months	38.5	25.8	12.7
Mean discounted overall survival	35.1	23.9	11.2
% Alive			
1 year	87%	72%	15%
2 years	68%	45%	22%
5 years	24%	12%	12%
QALYs, months	27.03	17.47	9.6
Costs			
Velcade and/or HDD	£21,942	£82	£21,860
Other care	£16,119	£10,808	£5,311
Adverse events	£1,463	£703	£760
Total	£39,524	£11,593	£27,931
Cost per discounted LYG			£29,906
Per QALY gained			£35,059

3.1.2.3 First Relapse Combination plus Stopping Rule

The combination of adding dexamethasone to bortezomib and limiting the number of cycles of bortezomib in non-responding patients reduces the cost per QALY still further to £30,586.

Table 13: The cost effectiveness results of 1st Relapse Combination with Stopping Rules

Outcomes	Velcade + HDD	HDD	Difference Velcade+HDD v HDD
Mean overall survival, months	36.7	25.8	10.9
Mean discounted overall survival	33.5	23.9	9.6
% Alive			
1 year	79%	72%	7%
2 years	64%	45%	19%
5 years	23%	12%	11%
QALYs, months	25.90	17.47	8.4
Costs			
Velcade and/or HDD	£16,281	£82	£16,199
Other care	£15,334	£10,808	£4,526
Adverse events	£1,463	£703	£760
Total	£33,078	£11,593	£21,485
Cost per discounted LYG			£26,961
Per QALY gained			£30,586

3.1.3 Scenario Analysis - Multi-use of bortezomib vials

The ERG within their report propose that the cost of a course of bortezomib treatment could be reduced if more than one patient were to be treated with bortezomib on the same day based on the ability to multi share vials. We thought that this was an interesting suggestion and have looked at an additional scenario within the model to understand the impact of multi-use vials on the cost effectiveness of bortezomib in routine clinical practice. Current rates of multi-use vials associated with bortezomib treatment within the NHS in England and Wales have been collected as part of a company sponsored market research study, which was conducted by a third party agency. This study involved a panel of Pharmacists and Haematologists who have used bortezomib within the last six months to ascertain the current multi-use of bortezomib vials occurs in approximately 15% of vials being shared at hospital centres in England and Wales.

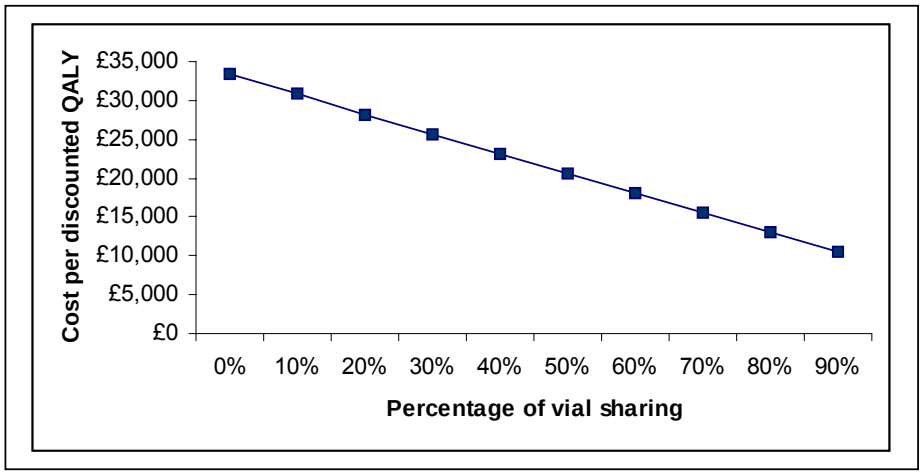
Based on the results of the market research study we have amended the cost of a course of bortezomib treatment to include multi use vials in the scenarios, which included the stopping rule, and in the scenario, which used both the stopping rule and bortezomib in combination with dexamethasone.

In estimating the cost of a course of bortezomib if multi use vials were used in the NHS in England and Wales we have assumed that two vials would be split between three patients.

3.1.3.1 First Relapse and Stopping Rule

Figure 3 shows the results of including vial sharing within the scenario of limiting the number of cycles of bortezomib treatment in non-responding patients at first relapse.

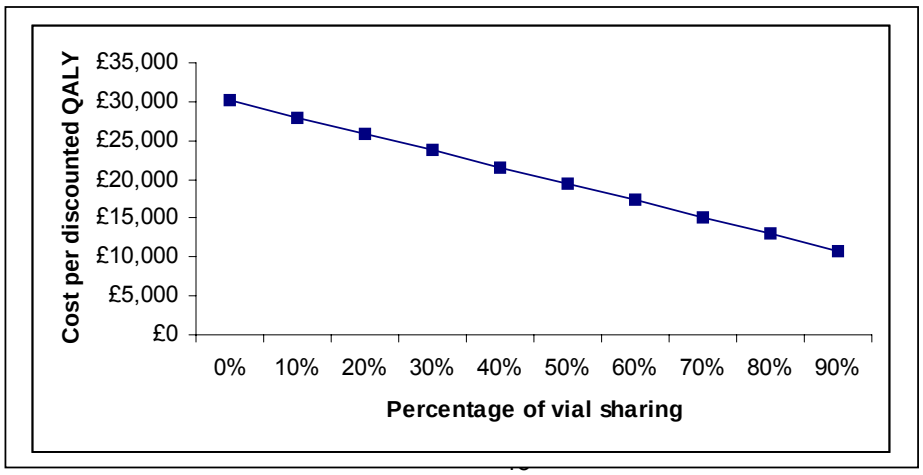
Figure 3: Impact of multi-use of vials on the cost effectiveness results of 1st Relapse plus Stopping Rule



In this analysis based on 15% of vials being multi-used we would expect that the cost per QALY would decrease from £33,515 to £30,112. This is based on a reduction of the cost of a course of bortezomib from £19,060 to £16,201.

3.1.3.2 First Relapse combination treatment:

Figure 4: Impact of multi-use of vials on the cost effectiveness results of 1st Relapse combination plus stopping rule Treatment



In this analysis based on 15% of vial being shared we would expect that the cost per QALY would decrease from £30,586 to £27,566.

In current clinical practice, the ability to vial share has been restricted by the lack of local funding for bortezomib treatment. This has made it practically difficult to get more two or more patients together at the same time. If the option of vial sharing was to move from 15% to 30% rates of which are seen in some other EU countries, the cost per QALY would then fall to £24,546.

3.2 Results of Sensitivity Analysis

3.2.1 One-Way Sensitivity Analysis

We have amended the key parameter ranges included within our one-way sensitivity analyses in line with those suggested by the ERG and added the cost of adverse events. We have considered within the sensitivity analyses first relapse combination plus stopping rule as this showed the most favourable cost effectiveness results. The results of these analyses are presented in Table 14 below.

Table 14: One-way sensitivity analysis results

		Inputs		CE ratios		Range
Variable	Basecase	Left	Right	Left	Right	
Duration of treatment effect, years	3	4	2	£27,363	£36,194	£8,831
Utilities - relative change	1	1	1	£26,583	£34,721	£8,138
Cost of other care - Velcade pre-progression	478	381	598	£27,064	£33,928	£6,864
Hazard ratio - TTP	£1	£1	£1	£27,774	£33,111	£5,336
Cost of other care - pre- and post-progression	477.53	381.48	597.77	£27,911	£31,871	£3,959
Cost of Velcade per course	£19,001	£18,096	£19,950	£29,036	£31,243	£2,207
Hazard ratio - OS	£1	£1	£1	£29,386	£30,971	£1,584
Cost of adverse events - relative change	1.00	1.25	0.75	£29,807	£30,417	£610
Cost of HDD per course	£82	£86	£78	£30,106	£30,118	£13

3.2.2 Probabilistic Sensitivity Analysis

We have used the same approach as that stated in Section 6.5.5.1 of the ERG report in that we have used the 95% confidence intervals for the hazard ratios and a range of +/- 25% for the costs. The results of the probabilistic sensitivity analyses are presented in Table 15 below.

Table 15: Probabilistic Sensitivity Analysis Results

Patient Group	Cost per QALY	95% CI
First relapse	£38,064	£33,236- £47,381
First relapse + stopping rule	£33,515	£28518 – £44,135
First relapse + Bortezomib + Dex	£35,059	£33,964-£47,540
First relapse + Bortezomib + Dex + stopping rule	£30,586	£28,678-£43717

First relapse + stopping rule + vial sharing	£30,112	£25,924 - £39,913
First relapse + bortezomib + dex + stopping rule + vial sharing	£27,566	£22,141 - £39,215

The results of the probabilistic sensitivity analyses show that across the scenarios considered within the model the lower 5th percentile is in the range of £22,000 to £29,000 per QALY. The upper 95th percentile ranges from £39,000 to £47,000 per QALY.

3.3 Discussion

The ERG concluded "in general the approach taken to model disease progression and cost effectiveness in this patient group seems reasonable" following their critique of our economic model. However, the ERG also raised some concerns regarding the model and we have addressed these concerns by providing this detailed response to all the specific comments raised within the ERG report and by revising to the economic model in line with the ERG proposals.

The ERG considers that the model may overestimate the treatment effect of bortezomib". We disagree with these comments and have shown in a comparison with the published incremental survival gain from APEX of 6 months (presented by Paul Richardson at the American Society of Haematology conference in December 2005 (ASH) (Please see figure below)), that it is clear that the results from the economic analysis do not represent an overestimation. It is important to note that in the published survival analysis of APEX that 62% of patients (208 patients) in the HDD crossed over to bortezomib when the study was halted prematurely on ethical grounds because of the superior benefits seen in the bortezomib arm. Therefore, the comparison of survival at 22 months follow-up in APEX is not a balanced comparison of bortezomib and HDD and should be considered as being bortezomib versus HDD followed by bortezomib. Given the superior TTP and response rates observed with bortezomib we believe that 9.9 months is likely to be a realistic, or even conservative estimate.

We agree with the ERG that Kumar is a good quality observational study and that this is the only published, credible long-term cohort data available for modelling progression in MM.

As stated in the ERG report, TTP is one of the two most important drivers of cost-effectiveness in the model (cost of bortezomib being the other). It is very important to understand that the TTP and 1-year survival rates for both Bortezomib and HDD were taken directly from the randomised phase of APEX and we are therefore highly confident that these are accurate and robust parameters to use in the modelling the effectiveness of HDD and Bortezomib.

The early termination of the APEX trial, however does affect the ability to model long-term outcomes and mortality data with Bortezomib and dexamethasone. The Kumar data was used for two reasons within our economic model. The first was to model the long-term **post progression** survival for both bortezomib and dexamethasone, and the second was to validate and calibrate the model in terms of overall mortality.

In our revised model we provide a full cost per QALY analysis incorporating the full set of changes that have been driven by the ERG critique. The results of the first relapse analysis show that the incremental cost per QALY of bortezomib at first relapse compared to HDD is £38,064, compared to £38,452 used in the original model. This shows that the ERG's proposed structural changes to our model do not impact the results to any significant degree.

The results of our scenario analyses confirm that the cost effectiveness of bortezomib was optimal when bortezomib was withdrawn in non-responders after three cycles. This reduced the cost per QALY by £4,549 to around £33,000. The analysis, which combined bortezomib plus dexamethasone with the stopping rule, reduces the cost per QALY still further to £30,556.

The results of the one-way sensitivity analysis show that there is no one parameter driving the model.

We have investigated in a market research study the impact of multi-use of bortezomib vials on the cost effectiveness of bortezomib in routine clinical practice. The results confirmed that vial sharing currently occurs in approximately 15% of hospital centres in England and Wales. We have amended the cost of a course of bortezomib treatment to include vial sharing in the scenarios, which included the stopping rule, and in the scenario, which used both the stopping rule and bortezomib in combination with dexamethasone. The results show that if multi-use of bortezomib was to take place in hospital centres equipped to do this in a safe manner that the cost per QALY would decrease. In the analysis, which included the stopping rule and vial sharing the cost per QALY falls to £30,112. The cost per QALY decreases even further to £27,566 when both the stopping rule and bortezomib in combination with dexamethasone is considered.

In summary, across these analyses the cost per QALY gained for bortezomib compared to HDD was £30,586 to £38,064 depending on the scenario. Once we include the possible scenario of multi-use of bortezomib vials, the cost per QALY estimates fall further. Sensitivity analyses revealed that the model was most sensitive to the hazard ratio for TTP and the cost of bortezomib treatment. We believe that bortezomib results in the greatest survival benefits and is most cost-effective when used at 1st relapse and when the number of cycles of bortezomib treatment is limited to three cycles in patients not responding to treatment. The model also confirms that the combination of dexamethasone adds over 1 month of survival for a very small additional cost.

4. References

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